

Application No. 10/056,528  
Amendment dated April 3, 2006  
Reply to final Office Action of February 3, 2006

### **REMARKS**

Favorable reconsideration of the subject application is respectfully requested in view of the above amendments and the following remarks. Following the amendments, claims 21, 25-29, 33, 36, 37, 41, 43, 45 and 47-53 are pending in the application, with claims 21 and 45 being in independent format.

Claim 21 has been amended to recite a method of treating migraine comprising administering an effective amount of a composition consisting essentially of a  $\text{Na}^+\text{K}^+\text{2Cl}^-$  cotransporter antagonist. Claim 27 has been amended to remove reference to ethacrynic acid. Claim 45 has been amended to correct language objected to by the Examiner. Claims 39, 40, 42, 44 and 56 have been cancelled from the application, and claims 47-51 and 53 have been amended to remove reference to cancelled claim 56.

It is urged that support for all the above amendments may be found throughout the specification as originally filed and that none of the amendments constitute new matter or raise new issues for consideration.

### **Claim Objections**

The Examiner objected to claims 45 and 56 as including improper Markush group language. Claim 45 has been amended as suggested by the Examiner. In addition, following the above amendments, claim 56 does not contain Markush group language.

### **Claim Rejections – 35 USC §102**

Claims 21, 27, 28, 36, 37 and 45 stand rejected under 35 USC §102(b) as being anticipated by Mathew et al. (*Neurology* 46:1226-1230, 1996). This rejection is respectfully traversed.

As noted previously, Mathew et al. studied patients with refractory transformed migraine type of chronic daily headache (CDH), and showed that a *subset* of these patients who were treated after diagnosis of increased intracranial pressure with a combination of antimigraine agents, acetazolamide and furosemide showed reduced number of days of severe headache and overall improvement in quality of life. Mathew et al. clearly state that the furosemide was administered to reduce increased intracranial pressure.

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Mathew et al. do not teach a method for the treatment of migraine comprising administering a composition consisting essentially of an effective amount of a  $\text{Na}^+\text{K}^+\text{2Cl}^-$  cotransporter antagonist as recited in amended claim 21, nor do they teach methods for treating migraine by administering a cation chloride cotransporter antagonist selected from the consisting of thiazide and thiazide-like compositions as recited in amended claim 45.

Applicant thus submits that Mathew et al. do not teach or suggest the presently claimed methods and that this rejection of the claims under 35 USC §102(b) may be properly withdrawn.

Claims 21, 27, 28, 36, 37, 45, 48, 49 and 56 stand rejected under 35 USC §102(b) as being taught by US Patent 5,753,651 to dePadova. This rejection is respectfully traversed.

As noted above, claim 56 has been cancelled from the application. dePadova teaches the use of angiotensin II subtype 1 (AT1) antagonists to treat sympathetically mediated pain and/or the symptoms of PMS. The reference states that AT1 antagonists may be administered in combination with other drugs, such as diuretics, including furosemide, bumetanide and/or ethacrynic acid. dePadova does not teach or suggest methods for the treatment of migraine by administering a composition consisting essentially of a  $\text{Na}^+\text{K}^+\text{2Cl}^-$  cotransporter antagonist as recited in independent claim 21 or by administering a cation chloride cotransporter antagonist selected from the group consisting of thiazide and thiazide-like compositions, as recited in claim 45.

It is thus submitted that the teachings of dePadova do not teach or suggest the presently claimed invention and that this rejection of the claims under 35 USC §102(b) may thus be properly withdrawn.

#### Claim Rejections – 35 USC §103

Claims 25, 26, 29, 33, 41, 43 and 47-53 stand rejected under 35 USC §103(a) as being unpatentable over Mathew et al. in view of Levin (US Patent 6,432,986), Bentley et al. (US Patent 6,369,094) and Becker et al. (US Patent 5,256,687). This rejection is respectfully traversed.

The teachings of Mathew et al. are discussed above. The Examiner states that Levin and Bentley et al. demonstrate the routine knowledge in the art of various methods of delivery, formulations and dosage forms for anti-migraine agents, and further that Becker et al.

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demonstrates the routine knowledge in the art of using mannitol as a carrier for furosemide. However none of these references overcome the deficiencies of Mathew et al. discussed above.

It is submitted that neither Mathew et al., Levin, Bentley et al. nor Becker et al., taken either singly or in combination, teach or suggest the presently claimed methods and that this rejection of claims 25, 26, 29, 33, 41, 43 and 47-53 under 35 USC §103(a) may thus be properly withdrawn.

Claims 25, 26, 33, 39-44 and 47-53 stand rejected under 35 USC §103(a) as being unpatentable over dePadova in view of Levin and Bentley. This rejection is respectfully traversed.

The teachings of all these references are discussed above. Neither Levin nor Bentley overcome the deficiencies of dePadova. It is therefore urged that none of these references, taken either singly or in combination, teach or suggest the presently claimed invention, and that this rejection of the claims under 35 USC §103(a) may thus be properly withdrawn.

Claims 25, 26, 33 and 53 stand rejected under 35 USC 103(a) as being unpatentable over Mathew et al. in view of Read et al. (Cephalalgia, December 1997, 17:826-832). Specifically, the Examiner asserts that Read "teaches the use of furosemide as *potential* agent for the treatment of migraine therapy" [emphasis added] and that the teachings of Mathew et al. and Read et al. would have rendered obvious the use of furosemide alone to treat migraine. This rejection is respectfully traversed.

As discussed in the Amendment and Reply filed on November 24, 2004, applicant's research indicates that the December 1997 issue of Cephalalgia was not received by any subscriber on or before the December 23, 1997 priority date of the present application, and that the Read et al. reference is therefore not prior art to the present application. Applicants note that the courts have held that there can be no rejection under 35 USC §102(a) if there is no proof that a reference was accessible to any member of the public prior to the filing date of an application (Carella v. Starlight Archery 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); see MPEP 2128). Applicants submit that there is no proof that the Read et al. reference was available to any subscriber before the priority date of December 23, 1997.

Even if further investigation were to show that selected subscribers *did* receive the December 1997 issue of Cephalalgia prior to the December 23, 1997, priority date, it is

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submitted that combining the teachings of Mathew et al. and Read et al. would not have rendered applicant's claimed methods obvious to one of skill in the art at the time the application was filed.

As discussed previously, Mathew et al. describe studies in which administration of a combination of both furosemide and acetazolamide together with known anti-migraine agents lead to improved control of symptoms in a subset of patients with refractory transformed migraine type of chronic daily headache (CDH) who had also been identified as having increased intracranial pressure (also referred to as idiopathic intracranial hypertension; ITH). Mathew et al. conclude that their observations indicate a *possible* link between migraine and ITH. Mathew et al. do not teach or suggest that administration of furosemide and/or acetazolamide in the absence of conventional anti-migraine agents would be effective in relieving the symptoms of migraine.

Read et al. present experimental data showing that furosemide inhibits regenerative cortical spreading depression in anaesthetized cats, and speculate that compounds with the ability to modify cortical spreading depression *may* have potential as anti-migraine compounds. While one of skill in the art, at the time the application was filed, *might* have been motivated to combine the teachings of Mathew et al. with those of Read et al., applicant submits that the combined teachings would not have led one of skill in the art to reasonably believe that furosemide *alone* could be *successfully* employed in the treatment of migraine. It was not until applicant's elucidation of the role of  $\text{Na}^+\text{K}^+\text{2Cl}^-$  cotransporter antagonists in modulating (reducing) the synchronization of neuronal population activity that is associated with seizure disorders and migraine headaches, that one of ordinary skill in the art would have had any reasonable expectation of success in employing  $\text{Na}^+\text{K}^+\text{2Cl}^-$  cotransporter antagonists, such as furosemide, in the treatment of migraine headaches and symptoms.

It is thus urged that neither the teachings of Mathew et al. nor those of Read et al., taken either singly or in combination, would have rendered the presently claimed methods obvious to one of skill in the art at the time the application was filed, and that the rejection of claims 25, 26, 33 and 53 under 35 USC §103(a) may thus be properly withdrawn.

#### Claim Rejections – Double Patenting

The pending claims stand provisionally rejected under the doctrine of obviousness type

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double patenting over claims 12-18 of copending Application no. 11/101,000. Specifically, the Examiner states that "migraine headaches" falls under the term neuropsychiatric disorders. While this is a provisional rejection, applicant strenuously disagrees with the Examiner's position. Should the Examiner wish to maintain this rejection, applicant respectfully requests that the Examiner provide evidence supporting the assertion that migraine is a neuropsychiatric disorder.


**Conclusion**

Every effort has been made to put the claims in condition for allowance. Early reconsideration and allowance of the pending claims is respectfully requested. If the Examiner has any further concerns regarding the application, he is invited to telephone the undersigned at 206.382.1191.

**Charge Deposit Account**

Please charge any additional fees that may be required, or credit any overpayment, to our Deposit Account No. 19-3555.

Respectfully submitted,

  
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